## REMARKS

Claims 1 - 102 were pending in the application. Claims 1 – 54, 66, 68 – 70, 72 – 76, 80, 84, 86 and 92 – 102 are cancelled. Claims 62, 77 and 78 have been withdrawn. Claims 55-65, 67, 71 and 75-91 are under examination. Claims 55, 58, 59, 60, 61, 67, 71, 75, 79, 83, 84 and 90 have been amended. New claims 103-105 have been added. No new matter has been added by virtue of the amendments and claims, support being found throughout the specification and claims as originally filed. In particular, support for the amendment to claim 55 and claim 60 can be found at paragraph [0112] of the published application. Support for the amendment to claim 90 can be found at paragraph [0204] of the published application. Support for new claim 103 is found at paragraph [0034] of the published application. Support for new claims 104 and 105 are found in original claims 55 and 60 and in FIGs. 1C, 3C, 10B and the descriptions thereof.

Any cancellation of the claims should in no way be construed as acquiescence to any of the Examiner's rejections and was done solely to expedite the prosecution of the application. Applicant reserves the right to pursue the claims as originally filed in this or a separate application(s).

**Rejection of Claims 55 – 62, 64, 65, 67, 71 and 75, 76, and 79 - 91 Under 35 USC 112, Second Paragraph**

The Examiner has rejected claims 55 – 62, 64, 65, 67, 71 and 75, 76, and 79 - 91 under 35 USC 112, second paragraph for alleged indefiniteness. Applicants respectfully traverse the rejection.

The Examiner argues that "claims 55 and 60 in particular are confusing and ambiguous in their recitation of the claimed microfluidics system, so that the structure of the claimed apparatus cannot be understood." (Office Action, p.2).

The Examiner first argues that "claim 55 recites a solid, planar substrate and material having at least one raised aperture with a tip and comprising a measurement chamber with a microchannel. But, the substrate and the material appear to be the

same component and it is not clear what the difference is." (Office Action, p.2). The Examiner argues further that "(i)t is not clear if the substrate/material is a one-piece device or a two piece device." (Office Action, p.2).

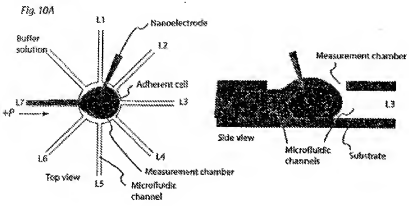
Applicants respectfully disagree. However, in the interest of expediting prosecution and without acquiescing to the Examiner's rejection, Applicants have herein amended claim 55 and claim 60 to recite that the substrate comprises **at least one measurement chamber for containing one or more cells or lipid based cell structures, the measurement chamber comprising at least one raised aperture (claim 55) or a plurality of solid electrode tips (claim 60).** Further, Applicants have herein included new claims 104 and 105 which clearly convey that the least one raised aperture or plurality of extends from a substantially planar portion of the measurement chamber. This is clearly described in FIGs. 1C, 3C, 10B and the descriptions thereof.

The Examiner next argues that "it is not clear what the measurement chamber is." (Office Action, p.3). Further the Examiner feels that the parts of the substrate, e.g. the microchannel and the measurement chamber, need to be "connected". The Examiner argues "(a)dditionally, the microchannel need not be connected to anything but the measuring chamber, and the measuring chamber need not be connected to anything." (Office Action, p.3). Applicants disagree.

As the Examiner is aware, "[t]he essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity. Definiteness of claim language must be analyzed, not in a vacuum, but in light of: (A) The content of the particular application disclosure; (B) The teachings of the prior art; and (C) The claim interpretation that would be given by one possessing the ordinary level of skill in the pertinent art at the time the invention was made.

Applicants note that according to the invention as claimed, the substrate comprises the microchannels that open into the measuring chamber that holds cells or cell structures. This is clearly conveyed by the application's disclosure. For Example, Figure 10 describes the configuration of the microchannels and chamber, where "as can be seen in FIG. 10A, the chip comprises a substrate with a plurality of microfluidic

channels whose inlets are radially disposed about the circumference of a measurement chamber." ([0093]). Figure 10A is shown below:



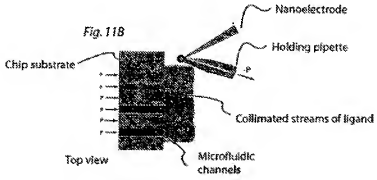

Further, Figure 11, as described at paragraph [0094] shows "**a substrate comprising a plurality of channels which feed into a cell chamber** is placed in proximity to a nanoelectrode and holding pipette (and) (t)he nanoelectrode is used to measure the electrical properties of the cell as it is scanned across **microchannel inlets that open into the cell chamber** ." Accordingly, the structure, interaction between the microchannel and cell chamber and how the claimed apparatus is used are clearly taught by the instant specification. Furthermore, contrary to the Examiner's assertion, a measurement chamber is well defined. The specification teaches that:

> As used herein, a "cell chamber" or a "measurement chamber" refers to an area formed by walls (which may or may not have openings) surrounding a base. A chamber may be "open volume" (e.g., uncovered) or "closed volume" (e.g., covered by a coverslip, for example) and may additionally comprise outlets in one or more walls from at least one microchannel. It is not intended that the geometry of the cell chamber be a limiting aspect of the invention. One or more of the wall(s) and/or base can be optically transmissive. Generally, a measurement chamber ranges in size but is at least about 1 μm. In one aspect, the dimensions of the chamber are at least large enough to receive at least a single cell, such as a mammalian cell. The chamber also can be a separate entity from the substrate comprising the microchannels. For example, in one aspect, the measurement chamber is a Petri dish and the microchannels extend to a surface of the substrate opening into the Petri dish so as to enable fluid

communication between the microchannels and the Petri dish. As used herein, the term "reservoir" and "measurement chamber" may be used interchangeably where measurements can be obtained in the reservoir/measurement chamber.

The Examiner further argues that "claim 90 is confusing because the phrase 'scanning a cell across the aqueous streams from the microchannels' is unclear' (and) it cannot be determined where the cell is in the claimed microfluidics system." (Office Action, p.3).

First, Applicants direct the Examiner to Figure 11B, below, which describes a cell as it is **scanned across microchannel inlets** that open into the cell chamber. Figure 11B is shown below:




However, in the interest of advancing prosecution, and without acquiescing to the validity of the Examiner's rejection, Applicants have amended claim 90.

In light of the above, Applicants respectfully request the Examiner withdraw the rejection of claims 55 – 62, 64, 65, 67, 71 and 75, 76, and 79 - 91 under 35 U.S.C. 112, second paragraph for alleged indefiniteness.

**Rejection of Claims Under 35 USC 102(b)**

The Examiner has rejected claims 55, 57 – 59, 67 and 71 under 35 USC 102(b) as being anticipated by Dollegast (US 5,078,164; the '164 reference herein). Applicants respectfully traverse the rejection.

Claim 55, as amended, recites a microfluidic system having a substrate, wherein the substrate has at least one measurement chamber for containing one or more cells or cell structures, the measurement chamber having at least one raised aperture for detecting an electrical property of one or more cells or cell structures, each aperture comprising a tip, the tip comprising a housing defining a lumen, wherein at least one tip is inserted into a cell or cell structure, and wherein the substrate has at least one microchannel with an outlet which opens into the at least one measurement chamber.

To anticipate a claim, each and every element of the claim must be found in a single reference. This is discussed in the Manual of Patent Examining Procedure § 2131:

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). "The identical invention must be shown in as complete detail as is contained in the . . . claim." Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). The elements must be arranged as required by the claim, but this is not an ipsissimis verbis test, i.e., identity of terminology is not required. In re Bond, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The '164 reference does not teach or suggest all the limitations of the instant claims. In particular, the '164 reference does not teach or suggest a microfluidic system as described by the instant claims, where the microfluidic system comprises a substrate having at **least one measurement chamber** for containing one or more cells or cell structures, **the measurement chamber having at least one raised aperture for detecting an electrical property of one or more cells or cell structures**, each aperture comprising a tip, the tip comprising a housing defining a lumen, **wherein at least one tip is inserted into a cell or cell structure, and wherein the substrate has at least one microchannel with an outlet which opens into the at least one measurement chamber.**

Nowhere does the '164 reference, expressly or inherently, teach or describe the microfluidic system as claimed, and in particular, a microfluidic system with a substrate with at least one measurement chamber **having at least one raised aperture for detecting an electrical property of one or more cells or cell structures and wherein at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate has at least one microchannel with an outlet which opens into the at least one measurement chamber.** The '164 reference is directed to a **microtiter plate washer**. In particular, the '164 reference describes a microtiter plate washer that comprises multiple upward-directed nozzles, each nozzle comprising a body member with an internal cavity and an orifice leading from the cavity to the exterior of the nozzle; a fluid distribution member having a fluid inlet and multiple fluid outlets, for distributing wash liquids to each nozzle; and clamping means for releasably sealing said nozzles to said fluid distribution member. (Col. 2, line 11). Applicants direct the Examiner's attention to Figure 1, shown below, and the accompanying description at col. 3, line 27:

> Figure 1 "shows a 2x2 plate washer with four nozzles for simplicity... Distribution box 10 comprises container walls 12 with inlet 14 in one container wall. The interior of distribution box 10 contains a series of ridges 16 and channels 18 spaced to provide support for later-described parts of the apparatus that will rest on the ridges. Channels 18 are spaced so as to allow fluid entering through aperture 14 to be distributed to each of the nozzles when they are in place in the apparatus.

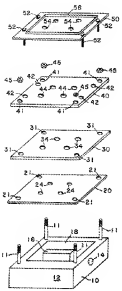


FIG. 1

Figure 8, below, is another view of a preferred embodiment of the invention.

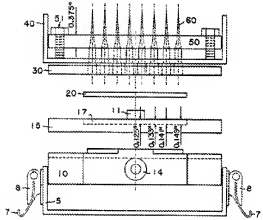


FIG. 8

As set forth in Figure 1 and Figure 8, and described by the Examiner, the '164 reference merely describes "a microfluidics systems comprising a microtiter plate attached to (clamped to) a microtiter plate washer for automated dispensing and washing of the contents of the wells of a microtiter place." (Office Action, p.3). As described by the Examiner, "(t)he microtiter plate comprises circular measurement chambers (and) the lid comprises an array of raised apertures with tips." Clearly, the microtiter plate washer does not comprise a substrate with at **least one measurement**

**chamber having at least one raised aperture for detecting an electrical property of one or more cells or cell structures and wherein at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate has at least one microchannel with an outlet which opens into the at least one measurement chamber.** Based on the foregoing; Applicants submit that the claims are not anticipated by the '164 reference

Accordingly, Applicants respectfully request withdrawal of the rejection and allowance of the claims.

The Examiner has rejected claims 60, 61, 62, 64, 65, 67, 75, 76, 79 – 83, 86 – 88 and 91 under 35 USC 102(b) as being anticipated by Peeters (US 6,123,819; the '819 reference herein). Applicants respectfully traverse the rejection.

Claim 60, as amended, recites a microfluidic system comprising a substrate, wherein the substrate comprises **at least one measurement chamber** for containing one or more cells or cell structures, **the measurement chamber comprising a plurality of solid electrode tips for detecting an electrical property of one or more cells or cell structures**, the tips having a housing defining a lumen, where the housing has a solid state conducting material, wherein **at least one tip is inserted into a cell or lipid based cell structure, and wherein the substrate further has at least one microchannel with an outlet which opens into the at least one measurement chamber**.

To anticipate a claim, each and every element of the claim must be found in a single reference (MPEP § 2131).

The '819 reference does not teach or suggest all the limitations of the instant claims. In particular, the '819 reference does not teach or suggest a microfluidic system as described by the instant claims, where the microfluidic system comprises a substrate with at least one measurement chamber for containing one or more cells or cell structures, the measurement chamber comprising **a plurality of solid electrode tips for detecting an electrical property of one or more cells or cell structures, the tips having a housing defining a lumen, where the housing has a solid state conducting material, wherein at least one tip is inserted into a cell or cell**

**structure,** and wherein the substrate further has at least one microchannel with an outlet which opens into the at least one measurement chamber.

Nowhere does the '819 reference, expressly or inherently, teach or describe the microfluidic system as claimed, and in particular, a microfluidic system as claimed with a plurality of solid electrode tips, **where the tips comprise a housing defining a lumen and wherein at least one tip is inserted into a cell or cell structure**.

**The present invention provides nanoelectrodes and nanotips that are used in ion channel recordings in cells or lipid based cell structures, i.e. for recording transmembrane currents in cells.** The claimed invention provides arrays of electrode devices having nanotips, where the nanotips comprise a tip portion that can be inserted into a cell for simultaneously or sequentially measuring the electrical properties of cells (e.g., such as surface immobilized cells).

FIG 1, below, shows schematics of nanotips used for intracellular recordings according to the invention as claimed. FIG. 1A shows an example of a hollow nanotip formed from a pulled capillary. FIG. 1B shows an array of pulled capillaries mounted together using a holder. FIG. 1C shows a one-dimensional array of microfabricated nanotips.

Figure 1

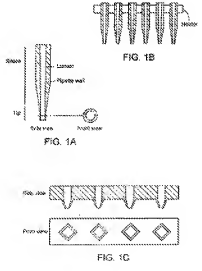



FIG. 1B

FIG. 1A

FIG. 1C

FIG 3, below, shows conducting solid-state material based nanoelectrodes according to the invention as claimed. FIG. 3A shows an example of a carbon fiber electrode coated with an insulating material to reduce measurement noise. The apex of the nanotip is uncoated in order to ensure electrical contact. FIG. 3B shows a silver-coated carbon-fiber nanoelectrode. FIG. 3C shows an example of microfabricated array solid-state nanoelectrodes.

Figure 3

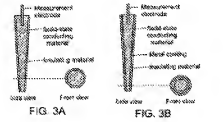



FIG. 3A FIG. 3B

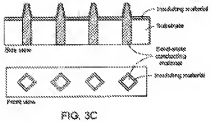



FIG. 3C

As shown in FIG 3, the housing can be filled with a solid electrically conducting medium for use in the electromeasurement. Further, figures 5-8 illustrate the insertion of the nanotips into cells and lipid based cell structures.

The '819 reference is directed to a nanoelectrode arrays that are used for detecting small biological molecules. In particular, the '819 reference describes a sensor which is capable of distinguishing between different molecular structures in a mixture. Each binding site includes nanometer scale points which extend above the surface of a substrate. These points are preferably nanoelectrodes which are spatially **configured to provide a three-dimensional electro-chemical binding profile which mimics a chemical binding site. Thus, the binding sites have selective affinity for a complementary binding site on a target molecule or for the target molecule**

**itself.** (col 2 – 3). Thus, the '819 reference is not directed to nanotips for insertion into cell or lipid based cell structure and for the detection of the electrical properties of these, but rather provides a three-dimensional electro-chemical binding profile which mimics a chemical binding site for a **protein or DNA molecule.**

Further, the '819 reference nowhere teaches **tips that comprise a housing defining a lumen and wherein at least one tip is inserted into a cell or lipid based cell structure**.

Applicants direct the Examiner to the description of the nanoelectrodes, at column 5, beginning at line 20, where the "(e)lectrodes 26a, 26b and 26c can be formed of a number of materials, either intrinsic or doped, such as gold and platinum and copper and other electrometals." Further, the '819 reference teaches only binding to the electrodes, where "several types of binding or adsorption of the molecule to the nanoelectrode receptor are possible, depending on the chemical composition of the nanoelectrodes, the voltage and the chemical to be measured. Binding forces may include covalent binding, electrostatic binding, hydrogen bonds and van der Waals bonds." (col 6, line 13). Nowhere does the '819 reference suggest any insertion of electrodes into cells, nor would the composition or arrangement of the electrodes facilitate such use.

Figure 1, below, for example shows a microelectronic molecular sensor 20 according to the '819 reference that has a substrate 22 on which an array of binding sites or clusters 24 are formed. Figure 2, also below, shows one binding site 24 in more detail as having multiple electrodes 26a, 26b and 26c which are spatially distributed to form a pattern. The '819 reference clearly teaches that the electrode on the substrate binds the selected proteins or DNA based molecules (see, e.g. claim 1) and is not used or contemplated to be used for insertion into a cell.

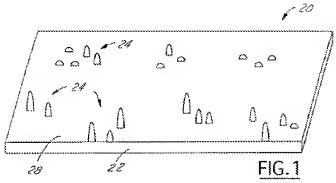



FIG. 1

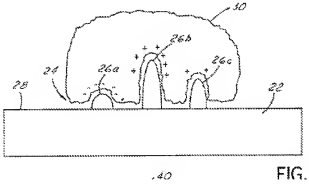



FIG. 2

The Examiner refers to Figure 5, shown below, which shows a "micro-channel 130 with a sample input port 132 and a long loop flowing into an optional reagent micro-chamber 134, itself connected to an optional input port 136. Micro-channel 130 separates biological molecules by size and charge while micro-chamber 134 allows the selective input of an external reagent or solution." (col 8, line 38).

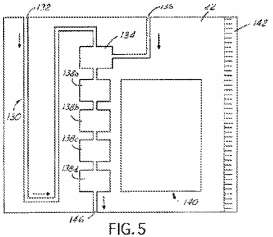



FIG. 5

The Examiner argues that "scanning of the nanoelectrode array at the x-y plane at specific positions is computer controlled...and may be performed with a laser. Thus, the laser can scan a cell structure such as a protein on the array relative to a microchannel outlet when the chip array of Figs. 1 – 3 is used in one of the chambers of Fig 5." (Office Action, p.5). In view of the arguments above, Applicants again point out that the '819 reference clearly teaches that the electrode on the substrate **binds** the selected biological molecule (proteins and DNA based molecules), and this "scanning" is substantially different from the scanning mechanism for scanning a cell or cell structure relative to a microchannel outlet as instantly claimed.

In light of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of the claims under 35 U.S.C. 102(b).

**Rejection of Claims Under 35 USC 103(a)**

Claims 55 – 62, 64, 65, 67, 71, 75, 76, and 79 - 91 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Peeters (the '819 reference, as above), in view of Chow et al. (US 5,800,690; the '690 reference herein). Applicants respectfully traverse the rejection.

The claims were set forth above.

The '819 reference fails to teach or suggest all the elements of the instant invention. In particular, the '819 reference does not teach or suggest a microfluidic system as claimed with raised apertures or a plurality of solid electrode tips (e.g., nanotips), **where the tips comprise a housing defining a lumen and/or are inserted into a cell or lipid based cell structure**. Further, the '819 fails to teach scanning a cell or lipid based cell structure relative to a microchannel outlet as instantly claimed.

The '690 reference does not cure the defects of the '819 reference. Nowhere in the '690 reference is there teaching or suggestion of **nanotips comprising a housing defining a lumen and wherein at least one tip is inserted into a cell or cell structure** as instantly claimed. Therefore, the teachings of the cited art, when combined, do not result in the claimed invention.

In light of the above, Applicants respectfully request the withdrawal of the rejection of claims 55 – 62, 64, 65, 67, 71, 75, 76, and 79 – 91 under 35 U.S.C. §103(a) for obviousness.

## CONCLUSION

In light of the above remarks, Applicants respectfully request early consideration and allowance of the subject application.

Should the Examiner wish to discuss any of the amendments and/or remarks made herein, the undersigned attorney would appreciate the opportunity to do so.

The Commissioner is hereby authorized to charge any fees that may be required, or credit any overpayment to Deposit Account No. **04-1105**.

Respectfully submitted,

Date: December 11, 2008

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